Consommation et Corporations Canada
Bureau des brevets
Ottawa, Canada
K1A 0C9

Consumer and Corporate Affairs Canada
Patent Office

(21) (A1) 2,020,802
(22) 1990/07/10
(43) 1991/01/13
(52) 167-164

5,029,8/46

(51) INTL.CL.^{5} A61K-9/66

(19) (CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Solid Dosage Form for Pharmaceutically Active Drugs

(72) Khanna, Satish C. - Switzerland ;

(73) Ciba-Geigy AG - Switzerland ;

(30) (CH) 2616/89-7 1989/07/12

(57) 22 Claims

Notice: The specification contained herein as filed

4-17661/=

Solid dosage form for pharmaceutically active drugs

Abstract of the Disclosure

The invention relates to a solid pharmaceutical dosage form from which the active drug or mixture of drugs is able to go quantitatively into solution under controlled conditions, immediately or continuously and substantially independently of the pH, i.e. of the concentration of hydrogen ions and hydroxyl ions and/or of other ions and also of enzymes of the ambient fluid, after a specific time, i.e. after expiry of a specific interval of time, characterised in that said dosage form, which contains an active drug or a mixture of drugs, a non-colloidal, water-swellable excipient (disintegrator) and at least one water-soluble excipient (osmosis-inducing compound), together with optional adjuncts, is coated with a semi-permeable membrane which, after passage through it of water of the ambient body fluid, opens like an eyelid (ruptures) after a specific predetermined time as a consequence of the pressure exerted by the swellable non-colloidal excipient and by the simultaneously induced osmotic pressure and by any gas pressure created internally, and releases the active drug or mixture of drugs quantitatively. The invention further relates to the preparation and use of the solid pharmaceutical dosage form.

4-17661/=

Solid dosage form for pharmaceutically active drugs

The present invention relates to a solid dosage form which is suitable for the controlled quantitative release of a pharmaceutically active drug or mixture of drugs substantially independently of of the pH, i.e. independently of the concentration of hydrogen ions and hydroxyl ions and/or of other ions such as phosphate ions and also enzymes of the ambient body fluid, into said ambient body fluid after a specific time, i.e. after expiry of a specific interval of time.

The oldest and best known form of administering a drug, that of oral administration, is still at the present time regarded as extremely convenient for introducing the pharmaceutical drug by immediate release into the blood circulation of the body, for example by immediate dissolution via the gastrointestinal tract. However, to ensure therapeutic effectiveness, such oral dosage forms have to be taken repeatedly at specific intervals during the day. As a consequence, further pharmaceutical dosage forms for peroral administration have been developed with delayed or repeated release of the drug (slow-release and sustained release forms) and also repeat forms, which make possible as constant, continuous and long-acting a drug concentration or also long-acting alternating drug concentration in the blood circulation as possible. The drug concentration, however, has been directly dependent on the physiological characteristics of the gastrointestinal fluids.

Although the slow-release and repeat dosage forms allow a continuous release of the drug in constant or alternating concentration, it has so far not proved possible to fulfil the need to provide a controlled, sudden, quantitative release of the drug after a specific time, i.e. after expiry of a specific interval of time, upon single or repeated administration, such that the intended release also occurs independently of the pH, i.e. of the concentration of hydrogen ions and hydroxyl ions and/or of other ions and enzymes.

Lachman et al. in "Theory and Practice of Industrial Pharmacy", pp. 430-465 (published by Lea and Febinger, Philadelphia, Pennsylvania, 1976), report that the drug release of the described dosage forms (slow-release and repeat forms) and also of other conventional

dosage forms is dependent on the solubility of the drug and this, in turn, is dependent on the pH of the ambient body fluid.

It is known that the solubility of many pharmaceutical drugs in dosage forms of the prior art, including slow-release and repeat forms, is very different in these pH ranges. Depending on their solubility, the drugs can be assigned to different classes, for example to the class of drugs which are distinguished by poor solubility or by insolubility in the low pH range of the stomach and by greater solubility in the higher pH range of the intestinal tract. Another class of drugs is characterised by solubility in the lower pH range and insolubility or poorer solubility in the higher pH range.

There are, however, also drugs whose solubility is strongly influenced by foreign ions, for example hydrogen ions and phosphate ions. Foreign ions can give rise to salting out effects or also to the precipitation of sparingly soluble salts, so that a complete release of the drug in the dosage form cannot take place.

German Offenlegungsschrift 1 617 724 discloses a dosage form coated with a film which, after a given time, is able to effect controlled release of the drug or mixture of drugs by rupture of the membrane. Rupture of the membrane is caused by the pressure of the colloidal swelling agent after diffusion of the body fluid into the drug core. The drugs used in this dosage form may be relatively readily soluble or also relatively sparingly soluble in the physiological fluids. Plasticisers may also additionally be used, for example glycerol, in order to facilitate the swelling of the colloidal swelling agent, for example gelatin. The dosage form disclosed in German Offenlegungsschrift 1 617 724 has, however, the drawback that the rupture of the membrane does not make the entire amount of drug immediately available because, after rupture of the mebrane, this latter still envelops the bulk of the drug and does not release it at once. Surprisingly, however, this drawback can be eliminated by causing osmotic pressure, in addition to the pressure exerted by swelling, to act upon the membrane, whereupon the membrane opens like an eyelid or a mussel shell, and the drug is immediately available quantitatively for release and is able to go immediately or, if in slow-release form, also continuously, into solution. If desired, the osmotic pressure applied in the practice of this invention can be further increased by gas pressure induced internally by the release of carbon dioxide by using, as osmosis-inducing excipients, salts of carbonic acid such as alkali metal or alkaline earth metal carbonates or hydrogencarbonates in the presence of a water-soluble organic acid, for example citric acid or tartaric acid. When water of the aqueous body fluid diffuses into the drug core, the

reaction between the above mentioned excipients releases carbon dioxide and, in addition to the osmotic pressure and the pressure exerted by swelling, a further mechanical pressure is produced by the internal gas pressure which acts upon the membrane.

The solid dosage form of this invention, from which the active drug or mixture of drugs is able to go into solution quantitatively, immediately or continuously and substantially independently of the pH, i.e. of the concentration of hydrogen ions and hydroxyl ions and/or of other ions and also of enzymes of the ambient fluid, under controlled conditions after a specific time, i.e. after expiry of a specific interval of time, is characterised in that said dosage form, which contains an active drug or a mixture of drugs, a non-colloidal, water-swellable excipient (disintegrator) and at least one water-soluble excipient (osmosis-inducing compound), together with optional adjuncts, is coated with a semi-permeable membrane which, after passage through it of water of the ambient body fluid, opens like an eyelid (ruptures) after a specific predetermined time as a consequence of the pressure exerted by the swellable non-colloidal excipient and by the simultaneously induced osmotic pressure and by any gas pressure created internally, and releases the drug or mixture of drugs quantitatively. Depending on its solubility, the drug or mixture of drugs can go into solution immediately or, if administered in slow-release form, also continuously.

The dosage form of this invention consists essentially of a film tablet (compressed tablet) or a pellet provided with an osmotically active core which, in addition to the drug or mixture of drugs and the non-colloidal swellable excipient, may also contain at least one water-soluble excipient (osmosis-inducing compound) and other adjuncts such as glidants and retarding agents, and with a semi-permeable membrane as film coating. As already stated above, the water-soluble excipients may comprise salts of carbonic acid such as alkali metal or alkaline earth metal carbonates or hydrogencarbonates and also organic water-soluble acids, for example citric acid. The dosage form may, however, also consist of a gelatin capsule which contains the active drug or mixture of drugs, the swellable excipient, at least one water-soluble excipient and other adjuncts such as glidants and retarding agents, in powder form, and which is coated with a semi-permeable membrane as film.

The semi-permeable membrane absorbs water at a specific rate which can be controlled by the composition and thickness of the membrane. The water of the ambient body fluid which has penetrated into the core dissolves the osmosis-inducing excipient and, in some

cases, the drug. An osmotic pressure is thereby created, which is all the greater the more molecules or ions go into solution. Normally an almost saturated solution forms.

In the simplest case, when water diffuses into the core the osmotic pressure, which also causes the swellable excipient to swell as secondary reaction, is partly produced by the active drug or mixture of drugs itself. However, this osmotic pressure by itself is not great enough to effect rupture of the membrane in the intended manner, so that the addition of at least one osmosis-inducing soluble excipient is essential. Should, however, the drug be poorly soluble or even insoluble in water, then a large amount of a water-soluble excipient must be added in order to produce the necessary osmotic pressure. The osmotic pressure necessary for inducing the working mechanism of the dosage form can thereby be created, so that the water which diffuses into the drug core and effects equalisation of the osmotic gradient causes the desired swelling of the swellable non-colloidal excipient (disintegrator) and, after a specific time, i.e. after expiry of a specific interval of time, the rupture of the membrane caused by the pressure induced by swelling and the osmotic pressure and any gas pressure produced internally for the release of the drug takes place.

The suitable semi-permeability of the membrane and the addition of a water-soluble excipient in the core of the tablet make it possible to prepare the dosage form of this invention substantially independently of the pH, i.e. of the concentration of hydrogen ions and hydroxyl ions and/or of other ions such as phosphate ions and also enzymes, for example in the digestive tract. In the extreme case, the solid dosage form of this invention for, for example, peroral administration, can also be used for drugs or mixtures of drugs which are sparingly soluble or even insoluble in a specific pH range of the gastrointestinal tract.

The time of release of the drug can be determined by
a) the water-permeability of the membrane film,
b) the film thickness,
c) the mechanical strength, i.e. elasticity and tensile strength of the membrane, and
d) the swelling properties of the swellable excipient present in the core and the ability of the excipient to induce an osmotic pressure by dissolution, and
e) the total surface area of the dosage form.
The time of release (time bomb) can be precisely manipulated by varying the different parameters a), b), c), d) and e).

In principle, all semi-permeable membranes which are known in the literature and have water-permeable properties are suitable for the preparation of the film of the dosage form of this invention.

Suitable semi-permeable membranes for the film layer are the semi-permeable membranes described, for example, in US patent specifications 3 916 889 and 3 997 404, and which are suitable for the passage of water of the ambient body fluid but not for the passage of the dissolved drug and hence are suitable for inducing osmosis. It is possible to use, for example, artificially prepared membranes from cellulose acetate, cellulose triacetate, agar acetate, amylose acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methylcarbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methylsulfonate, cellulose acetate butylsulfonate, cellulose ether, cellulose acetate propionate, cellulose acetate diethylaminoacetate, cellulose acetate octoate, cellulose acetate laurate, methyl cellulose, cellulose acetate p-toluenesulfonate, hydroxylated ethylene vinyl acetate, cellulose acetate butyrate, and from other cellulose acetate derivatives. Other suitable semi-permeable membranes are hydroxypropylmethyl cellulose and polymeric epoxides, copolymers of alkylene oxide and alkyl glycidyl ethers, polyglycols or polylactic acid derivatives and further derivatives. It is also possible to use mixtures, for example of basically water-insoluble acrylates (e.g. copolymer of ethyl acrylate and methacrylate).

The film-forming coating material (membrane) can be applied by any method, provided it results in a continuous film of substantially uniform thickness.

The coating, for example, of the tablet and also of the pellet with a film of the required thickness of a semipermeable membrane can be carried out in fluidised beds, in coating drums or also by means of a coacervation process.

Suitable swellable non-colloidal excipients (swelling agents or also disintegrators) are inert substances which swell rapidly on contact with aqueous fluids and are, for example, alginic acid and derivatives thereof, ultraamidopectins, cellulose such as microcrystalline or microfine cellulose, crosslinked carboxymethyl cellulose, carboxymethyl starch, modified starch, crosslinked polyvinylpolypyrrolidone, bentonite, veegum, montmorillonite, dried citrus pulp, xylanes and also cationic and anionic exchangers such as cholestyramine.

The water-soluble osmosis-inducing excipients may be those substances which are non-irritant to the stomach and intestinal mucosa and are, typically, inorganic and organic salts such as sodium chloride, sodium hydrogen phosphate, sodium nitrate and sodium acetate, or also alkali metal salts or alkaline earth metal salts of carbonic acid such as sodium or calcium carbonate or also sodium or calcium hydrogencarbonates, or also water-soluble organic acids such as tartaric acid, citric acid or also succinic acid, alone or in conjunction with the above carbonates and also sugars, especially, for example, mannitol, glucose, fructose, lactose and dextran compounds of different molecular weight for inducing the osmotic pressure or the osmosis necessary for inducing swelling. The amount of the excipient may vary from a fraction to a multiple of the amount of solid drug or mixture of drugs.

As optional adjuvants it is possible to use glidants such as magnesium stearate, silicon aerogel and, preferably, also talcum.

The film coating may contain, as optional adjuvants, for example pigments such as coloured iron oxides or titanium dioxide and/or flavourings such as sweeteners (for example saccharine, sodium cyclamate or sugar).

Suitable cores comprising drug or mixture of drugs and excipients are the compressed tablets, capsules and pellets conventionally known in galenics and which can be prepared by known methods. For example, the tablet material can be prepared by mixing the solid particles, i.e. of the drug or mixture of drugs, swelling agent, excipients and optional adjuncts such as glidants and, if required, retarders. The tablets and pellets can be prepared in the tabletting machines known for making, for example, round and rod-shaped mouldings and pellets, and the capsules are filled in known capsule-filling machines.

Retarders may be substantially water-insoluble adjuncts or mixtures thereof such as lipids, and fatty alcohols such as cetyl alcohol, stearyl alcohol and cetostearyl alcohol; glycerides such as glycerol monostearate or mixtures of mono-, di- and triglycerides of vegetable oils; hydrogenated oils such as hydrogenated castor oil or hydrogenated cottonseed oil; waxes such as beeswax or carnauba wax; solid hydrocarbons such as paraffin or mineral wax; fatty acids such as stearic acid; certain cellulose derivatives such as ethyl cellulose or acetyl cellulose; polymers or copolymers such as polyalkylenes, for example polyethylene, polyvinyl compounds such as polyvinyl chloride or polyvinyl acetate, as

well as vinyl chloride/vinyl acetate copolymers and copolymers with crotonic acid, or polymers and copolymers of acrylates and methacrylates, for example copolymers of ethyl acrylate and methyl methacrylate.

In particular, the invention relates to a solid dosage form for oral administration which is suitable for the controlled quantitative release of the drug or mixture of drugs after a specific time independently of of the pH, i.e. of hydrogen and hydroxyl ions and also of other ions, for example phosphate ions and enzymes in the gastrointestinal tract.

The dosage form of this invention can be used in particular whenever release of the drug or mixture of drugs shall follow repeatedly after several desired successive intervals of time, for example after the expiry of several hours. First and foremost, the solid pharmaceutical dosage form can be used whenever the release of drug shall follow after expiry of several identical intervals of time, i.e. periodically. For example, pellets which have been prepared by the method of obtaining the dosage form of this invention, but having a different time of and thus delayed release, can be administered in a single dosage form, for example a gelatin capsule. The release at different intervals can, as stated initially, be controlled precisely in accordance with the enclosed drawing (A) by the layer thickness of the membrane, the mechanical strength and elasticity of the membrane, and also by the amount and swelling properties of the swelling agent (disintegrator) and the osmosis-inducing property of the excipient or of the suitable excipients which produce carbon dioxide. The drawing shows that the release of the drug (diclofenac sodium) is effected after different intervals of time in conformity with the data in Table I of Example 1.

The expression "pharmaceutically active drug" employed herein will be understood as comprising all therapeutic agents, for example the therapeutic agents used in human and veterinary medicine.

The dosage form of this invention is suitable, for example, for water-soluble and also water-insoluble pharmaceutically active drugs which may be inorganic or, preferably, organic active compounds and which may be used in accordance with their indication as analgesics, antipyretics, antirheumatic agents, sedatives, hypnotics, antiepilectic agents, depressants and stimulants, neuroleptic agents, antihistamines, antihypertensives, anticoagulants, antithrombotic agents, psychotropic agents, psycholeptics, chemotherapeutic agents such as antibiotics, sulfonamides, antituberculosis agents

(tuberculostatic agents) or also chemotherapeutic agents for tropical infections, diuretics, spasmolytics, cardiovascular agents such as sympathomimetic agents, cardiac stumulants such as cardiac glycosides and digitaloids, parenteral glycotherapeutics, centrally acting analeptics, geriatric agents, tonolytics (of the striated muscles), antiparkinson drugs, cytostatics, immunosuppressants, tonics, hormones and vitamins according to B. Helwig (Moderne Arzneimittel), 1980.

Typical examples of antibiotics which may be used as solid active drugs for the dosage form of this invention are penicillin, tetracycline, chlortetracycline, bacitracin, nystatin, streptomycin, neomycin, polymicin, gramicidin, oxytetracycline, chloramphenicol, erythromycin, rifampicin, cefazoline, cefotoxin, cefsulodin, cefotiam and mefoxin; and examples of chemotherapeutic agents are sulfamethazine, sulfamerizine, sulfamethizole, and sulisoxazole. Further, examples of suitable sedatives and hypnotics which may be used are chloral hydrate, midazolam, pentabarbital, phenobarbital, secobarbital, codein and carbromal; and examples of cardiac glycosides and digitaloids are digitoxin and digoxin; and a suitable sympathomimetic is epinephrin as solid drug in water-soluble or water-insoluble form.

In particular, antipyretics, analgesics and antirheumatic agents may be used in appropriate water-soluble or water-insoluble form as solid active drug in the dosage form of this invention. Representative examples are: propyphenazone, aminophenazone, aspirin (ASA), antipyrine, methylnifenazine, melaminesulfone, sulfenazone, phenacetin, pentazozine, lactophenine, paracetamol, quinine, flufenamic acid, tolfenamic acid, meclofenamic acid, niflumic acid, clonoxine or clonixidine, flunixine, ibuprofen, suprofen, ketoprofen, fenoprefen, pirprofen, diclofenac, ibufenac, proctizinic acid, naproxen, cicloprofen, tolmetin, clopirac, tiaprofenoic acid, oxaprozine, fenclozinic acid, fentiazic, clidanac, fenclonac, fenoprofen, flurbiprofen, carprofen, sulindac, cinmetacin, fenbuten, etodolac, butifufen.

Psychotropic drugs, for example neuroleptics, antidepressives, thymoleptics, thymetics and tranquillizers, may conveniently be used in water-soluble or water-insoluble form as solid active drug in the dosage form of this invention, for example thioridazine, imipramine, desimiprimine, clomipramine, ketimipramine, opipramol, amitryptyline, nortryptyline, reserpine, aromazine, chlorpromazine, fluopromazine, methopromazine, trimeprazine, diethazine, promethazine, aminopromazine, mepazine, pipamazine and maprotiline.

In particular, analgesics and antirheumatic agents, for example ibuprofen, pirprofen, ibufenac, naptoxen and diclofenac, can be used in the dosage form of this invention. Most advantageously, diclofenac can be used as analgesic and antirheumatic agent in the dosage form of this invention.

It is also possible to use antihypertensives such as oxprenolol and metoprolol or also hypnotic drugs such as midazolam as solid active drug in the dosage form of this invention.

The following non-limitative Examples illustrate the invention in more detail. Parts are by weight, unless otherwise stated.

Example 1: A dosage form (film tablet) for oral administration which contains 50 mg of diclofenac sodium as active drug in the compressed core and is coated with a semipermeable membrane as film, and which releases the active drug after a predetermined time, is prepared as follows:

a) Preparation of the core:
The cores of the following composition are compressed in a tabletting press with only one punch using a 8 mm concave punch (R 12 mm):
Each compressed core contains:

diclofenac sodium	50 mg
polyvinylpyrrolidone (crosslinked):	100 mg
sodium chloride	50 mg
silica aerogel (Aerosil® 200)	7 mg
magnesium stearate	3 mg

The powder for 2000 tablet cores is homogeneously mixed for 20 minutes in an eccentric tumbler mixer (Turbulamixer) and compressed as described above to cores of 210 mg.

b) Preparation of the film coating:
1500 compressed cores are film-coated by the fluidised bed method with a semi-permeable film of the following composition:

cellulose acetate containing 32% of acetyl	46.5 g
cellulose acetate containing 32.9% of acetyl	48.5 g
hydroxypropylmethyl cellulose	5.0 g

Coating is effected with a solution containing an organic lacquer which contains 5% of solid lacquer component in a solvent mixture consisting essentially of 1800 ml of methylene chloride and 200 g of methanol. The cores are coated with layers of different strength (i.e. of different weight), for example with ca. 12 mg, 22 mg, 33 mg, 47 mg and 62 mg of lacquer, and are dried in a flow of air in a fluidized bed drier for 48 hours at 40°C.

c) Determining the release of active drug:
Film tablets of 5 different film strengths (coated with a film of different weight) are put into glass beakers (10 tablets per beaker) containing 200 ml of deionised water at 37°C, and the time until rupture of the 5 systems is determined. The values are reported in Table I.

Tabelle I

System	Weight of the lacquer	Time until rupture					
1	12 mg	57,	62,	64,	65,	75	($\bar{x}$ = 65; S_{rel} = 9.1)
2	22 mg	103,	110,	127,	128,	130	($\bar{x}$ = 120; S_{rel} = 9.2)
3	33 mg	159,	175,	178,	180,	188	($\bar{x}$ = 176; S_{rel} = 5.4)
4	47 mg	201,	201,	203,	217,	222	($\bar{x}$ = 209; S_{rel} = 4.3)
5	62 mg	387,	390,	293,	395,	430	($\bar{x}$ = 399; S_{rel} = 3.9)

Example 2: Ca. 5000 cores each containing 10 mg of oxprenolol succinate as active drug and having the following composition are compressed:

oxprenolol succinate	10 mg
sodium chloride	25 mg
cholestyramine USP	50 mg
silica aerogel	4.5 mg
magnesium stearate	0.5 mg

The cores of the above composition having a weight of ca. 90 mg are compressed using a 6 mm concave punch in a tabletting press with only one punch.

About 1000 compressed cores are coated by the fluidized bed method in a flow of air with a film consisting of 20 mg, 25 mg and 30 mg of lacquer. The film membranes consist of 40% by weight of a cellulose acetate having an acetyl content of 32% and of 55% by weight of a cellulose acetate having an acetyl content of 39.8% by weight and 5% by weight of hydroxypropylmethyl cellulose.

Coating is effected with a solution containing an organic lacquer which contains 5% of solid lacquer component in a solvent mixture consisting of methylene chloride and methanol in the ratio 9:1. The cores are coated with layers of different strength (i.e. of different weight), for example with ca. 20 mg, 25 mg, and 30 mg of lacquer, and dried in a flow of air in a fluidized bed drier for 24 hours at 40°C.

Determining the release of active drug:

Film tablets of 3 different film strengths (coated with a film of different weight) are put into glass beakers (10 tablets per beaker) containing 200 ml of deionised water at 37°C, and the time until rupture of the 3 systems is determined. The values are reported in Table II.

Tabelle II

System	Weight of the lacquer	Time until rupture
1	20 mg	118, 120, 125, 125, 130, 131, 132, 136, 140, 142 ($\bar{x} = 130$; $S_{rel} = 6.1$)
2	25 mg	147, 158, 159, 160, 166, 179, 180, 180, 184 ($\bar{x} = 167$; $S_{rel} = 7.2$)
3	30 mg	205, 209, 212, 212, 214, 215, 219, 219, 220, 222 ($\bar{x} = 215$; $S_{rel} = 2.4$)

Example 3: Ca. 1000 cores each containing 7 mg of midazolam (Dormicum®) as active drug and having the following composition are compressed:

midazolam	7 mg
sodium chloride	50 mg

polyvinylpyrrolidone (crosslinked) 100 mg
silica aerogel 7 mg
magnesium stearate 2.0 mg

The cores of the above composition having a weight of ca. 165 mg are compressed using a 8 mm concave punch in a tabletting press with only one punch.

Compressed cores are coated by the fluidized bed method in a flow of air with a film consisting of 38 mg of lacquer. The film membranes consist of 46.5% by weight of a cellulose acetate having an acetyl content of 32% and of 48.5% by weight of a cellulose acetate having an acetyl content of 39.8% and 5% by weight of hydroxypropylmethyl cellulose.

Coating is effected with a solution containing an organic lacquer which contains 5% of solid lacquer component in a solvent mixture consisting of methylene chloride and methanol in the ratio 8:2. The cores are coated with layer of 38 mg of lacquer and dried in a flow of air in a fluidized bed drier for 24 hours at 40°C.

Determining the release of active drug:
10 film tablets are put into a glass beaker containing 200 ml of deionised water at 37°C, and the time until rupture of the systems is determined. The values are reported in Table III.

Tabelle III

System	Weight of the lacquer	Time until rupture
1	38 mg	250, 250, 252, 260, 260, 264, 270, 272, 275, 280 ($\bar{x} = 263$; $S_{rel} = 6.8$)

What is claimed is:

1. A solid pharmaceutical dosage form from which the active drug or mixture of drugs is able to go quantitatively into solution under controlled conditions, immediately or continuously and substantially independently of the pH, i.e. of the concentration of hydrogen ions and hydroxyl ions and/or of other ions and also of enzymes of the ambient fluid, after a specific time, i.e. after expiry of a specific interval of time, characterised in that said dosage form, which contains an active drug or a mixture of drugs, a non-colloidal, water-swellable excipient (disintegrator) and at least one water-soluble excipient (osmosis-inducing compound), together with optional adjuncts, is coated with a semi-permeable membrane which, after passage through it of water of the ambient body fluid, opens like an eyelid (ruptures) after a specific predetermined time as a consequence of the pressure exerted by the swellable non-colloidal excipient and by the simultaneously induced osmotic pressure and by any gas pressure created internally, and releases the active drug or mixture of drugs quantitatively.

2. A solid pharmaceutical dosage form according to claim 1, which consists of a film tablet or a pellet having an osmotic active core which, in addition to containing the active drug or mixture of drugs and the non-colloidal swellable excipient, may also contain at least one water-soluble excipient (osmosis-inducing compound) and other adjuncts such as glidants and retarding agents, and is provided with a semi-permeable membrane as film coating.

3. A solid pharmaceutical dosage form according to claim 1, which consists of a capsule which contains, in powder form, the active drug or mixture of drugs, the swellable non-colloidal excipient, at least one water-soluble carrier and other adjuncts, and is coated with a semi-permeable membrane as film.

4. A solid pharmaceutical dosage form according to claim 1 or claim 3, which consists of a gelatin capsule which contains, in powder form, the active drug or mixture of drugs, the swellable non-colloidal excipient, at least one water-soluble carrier and other adjuncts, and is coated with a semi-permeable membrane as film.

5. A solid pharmaceutical dosage form according to any one of claims 1 to 4, wherein the swellable non-colloidal excipient in said solid dosage form is an inert substance which

swells rapidly upon contact with aqueous fluids.

6. A solid pharmaceutical dosage form according to any one of claims 1 to 5, wherein the swellable non-colloidal excipient in said solid dosage form is selected from the group consisting of alginic acid and derivatives thereof, ultraamidopectins, cellulose such as microcrystalline or microfine cellulose, crosslinked carboxymethyl cellulose carboxymethy starch, modified starch, crosslinked polyvinylpolypyrrolidone, bentonite, veegum, montmorillonite, dried citrus pulp, xylanes and also cationic and anionic exchangers.

7. A solid pharmaceutical dosage form according to any one of claims 1 to 6, wherein the swellable non-colloidal excipient in said solid dosage form is crosslinked polyvinyl polypyrrolidone or cholestyramine.

8. A solid pharmaceutical dosage form according to any one of claims 1 to 4, wherein the excipient (osmosis-inducing compound) is selected from the group consisting of water-soluble inorganic or organic salts such as sodium chloride, sodium hydrogen phosphate, sodium nitrate and sodium acetate, or also alkali metal salts or alkaline earth metal salts of carbonic acid such as alkali metal or alkaline earth metal carbonates or hydrogencarbonates, or also water-soluble organic acids such as tartaric acid, citric acid or also succinic acid, alone or in conjunction with the above carbonates and also sugars, especially, for example, mannitol, glucose, fructose, lactose and dextran compounds of different molecular weight.

9. A solid pharmaceutical dosage form according to any one of claims 1 to 4, wherein the semi-permeable membrane used as film coating of said solid dosage form is a membrane which is suitable for the passage of water of the ambient body fluid but not for the passage of the dissolved active drug.

10. A solid pharmaceutical dosage form according to any one of claims 1 to 4 and 9, wherein the semi-permeable membrane used as film coating is an artificially prepared membrane from cellulose acetate, cellulose triacetate, agar acetate, amylose acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methylcarbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methylsulfonate, cellulose acetate butylsulfonate, cellulose ether,

cellulose acetate propionate, cellulose acetate diethylaminoacetate, cellulose acetate octoate, cellulose acetate laurate, methyl cellulose, cellulose acetate p-toluenesulfonate, hydroxylated ethylene vinyl acetate, cellulose acetate butyrate, hydroxypropylmethyl cellulose and polymeric epoxides, copolymers of alkylene oxide and alkyl glycidyl ethers, polyglycols or polylactic acid derivatives and from acrylates (for example the copolymer of ethyl acrylate and methacrylate).

11. A solid dosage form according to any one of claims 1 to 9, wherein the active drug or mixture of drugs is selected from the group consisting of analgesics, antipyretics, antirheumatic agents, sedatives, hypnotics, antiepilectic agents, depressants and stimulants, neuroleptic agents, antihistamines, antihypertensives, anticoagulants, antithrombotic agents, psychotropic agents, psycholeptics, chemotherapeutic agents such as antibiotics, sulfonamides, antituberculosis agents (tuberculostatic agents) or also chemotherapeutic agents for tropical infections, diuretics, spasmolytics, cardiovascular agents such as sympathomimetic agents, cardiac stumulants such as cardiac glycosides and digitaloids, parenteral glycotherapeutic agents, centrally acting analeptics, geriatric agents, tonolytics (of the striated muscles), antiparkinson drugs, cytostatics, immunosuppressants, tonics, hormones and vitamins according to B. Helwig (Moderne Arzneimittel), 1980.

12. A solid pharmaceutical dosage form according to any one of claims 1 to 9, wherein the active drug is selected from the group consisting of penicillin, tetracycline, chlortetracycline, bacitracin, nystatin, streptomycin, neomycin, polymicin, gramicidin, oxytetracycline, chloramphenicol, erythromycin, rifampicin, cefazoline, cefotoxin, cefsulodin, cefotiam and mefoxin.

13. A solid pharmaceutical dosage form according to any one of claims 1 to 9, wherein the active drug is a chemotherapeutic agent such as sulfamethazine, sulfamerizine, sulfamethizole, and sulfisoxazole.

14. A solid pharmaceutical dosage form according to any one of claims 1 to 9, wherein the active drug is a sedative or hypnotic agent selected from the group consisting of chloral hydrate, midazolam, pentabarbital, phenobarbital, secobarbital, codein and carbromal.

15. A solid pharmaceutical dosage form according to any one of claims 1 to 9, wherein the

active drug is a cardiac glycoside or digitaloid such as digotoxin or digoxin.

16. A solid pharmaceutical dosage form according to any one of claims 1 to 9, wherein the active drug is a sympathomimetic agent such as epinephrin.

17. A solid pharmaceutical dosage form according to any one of claims 1 to 9, wherein the active drug is selected from the group consisting of antipyretics, analgesics and antirheumatic agents such as propyphenazone, aminophenazone, aspirin (ASA), antipyrin, methylnifenazine, melaminesulfone, sulfenazone, phenacetin, pentazozine, lactophenine, paracetamol, quinine, flufenamic acid, tolfenamic acid, meclofenamic acid, niflumic acid, clonoxine or clonixidine, flunixine, ibuprofen, suprofen, ketoprofen, fenoprefen, pirprofen, diclofenac, ibufenac, proctizinic acid, naproxen, cicloprofen, tolmetin, clopirac, tiaprofenoic acid, oxaprozine, fenclozinic acid, fentiazic, clidanac, fenclonac, fenoprofen, flurbiprofen, carprofen, sulindac, cinmetacin, fenbuten, etodolac, butifufen.

18. A solid pharmaceutical dosage form according to any one of claims 1 to 9, wherein the active drug is selected from the group consisting of analgesics and antirheumatic agents such as ibufprofen, pirprofen, ibufenac, naproxen and diclofenac.

19. A solid pharmaceutical dosage form according to any one of claims 1 to 9, wherein the active drug is diclofenac.

20. A solid pharmaceutical dosage form according to any one of claims 1 to 9, wherein the active drug is selected from the group consisting of neuroleptics, antidepressives, thymoleptics, thymeretics and tranquillizers, such as thioridazine, imipramine, desimiprimine, clomipramine, ketimipramine, opipramol, amitryptyline, nortryptyline, reserpine, aromazine, chlorpromazine, fluopromazine, methopromazine, trimeprazine, diethazine, promethazine, aminopromazine, mepazine, pipamazine and maprotiline.

21. A solid pharmaceutical dosage form according to any one of claims 1 to 9, wherein the active drug is midfazolam.

22. A process for the preparation of a solid pharmaceutical dosage form from which the active drug or mixture of drugs is able to go quantitatively into solution under controlled conditions, immediately or continuously and substantially independently of the pH, i.e. of the concentration of hydrogen ions and hydroxyl ions and/or of other ions and also of

enzymes of the ambient fluid, after a specific time, i.e. after expiry of a specific interval of time, which process comprises compressing the active drug or mixture of drugs, in the presence of a non-colloidal, water-swellable excipient (disintegrator) and at least one water-soluble excipient (osmosis-inducing compound), together with optional adjuncts such as glidants and retardants, to a pharmaceutical dosage form, for example a tablet or pellet, or encaspsulating it in powder form in a capsule, and coating said dosage form with a semi-permeable membrane which, after passage through it of water of the ambient body fluid, opens like an eyelid (ruptures) after a specific predetermined time as a consequence of the pressure exerted by the swellable non-colloidal excipient and by the simultaneously induced osmotic pressure and by any gas pressure created internally, and releases the active drug or mixture of drugs quantitatively.